Universidade de Lisboa

Faculdade de Farmácia

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A need to report immunogenicity data systematically

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Mestrado Integrado em Ciências Farmacêuticas

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Resumo

Objetivo: Analisar se a prática contemporânea de avaliação fármaco a fármaco resulta na inclusão suficiente de informação (relativa à imunogenicidade) nos Resumos de Características do Medicamentos (RCMs) de produtos biológicos aprovados no Espaço Económico Europeu.

Métodos: Informação relacionada com imunogenicidade foi identificada e extraída de um grupo de 73 medicamentos biológicos que cumpriam com critérios de seleção definidos *à priori*. Posteriormente, treze questões dicotómicas relacionadas com imunogenicidade foram propostas para avaliar se há assuntos que estão atualmente a ser negligenciados pelos RCMs destes produtos.

Resultados: A maioria dos RCMs (92%) não inclui recomendações direcionadas para médicos e/ou doentes sobre como reportar Reações Adversas ao Medicamento possivelmente causadas por imunogenicidade. Adicionalmente, 80% dos RCMs não identifica o método utilizado para determinar as taxas de imunogenicidade reportadas nestes documentos e 81% dos RCMs não possui informação quanto ao impacto que a imunogenicidade pode ter (ou não) na farmacocinética destes fármacos. Foi também identificado um fator de grupo em que RCMs de fármacos mais antigos poderão estar a influenciar como abordar e quais os assuntos abordados por RCMs de medicamentos mais recentes. Para transformar os RCMs de produtos biológicos em documentos úteis a consultar quando uma resposta imunogénica ocorre, é avançada uma proposta sobre como reportar sistematicamente informação relativa à imunogenicidade nestes documentos.

Conclusões: Com base nestes resultados, uma estratégia de avaliação fármaco a fármaco não resulta em RCMs com informação suficiente pelo que é necessário repensar esta abordagem e reportar estes dados de forma sistemática. Orientações futuras sobre como reportar informação relacionada com imunogenicidade serão necessárias, caso contrário os RCMs não serão a fonte base de informação, para profissionais de saúde, sobre como usar um produto biológico de forma segura e eficaz.

Palavras-Chave: Imunogenicidade; Anticorpos Anti Fármaco; Resumo das Características do Medicamento; Terapêutica Biológica; Espaço Económico Europeu

Abstract

Objective: To evaluate whether the current case-by-case practice leads to sufficient reporting of immunogenicity-related information in the Summary of Product Characteristics (SmPCs) of biological products approved in the European market.

Methods: Immunogenicity-related information was identified and extracted from a group of 73 biological drugs that complied with drug-selection criteria. Afterwards, thirteen dichotomous questions were proposed to evaluate whether any issues are being commonly neglected.

Results: Most SmPCs (92%) do not have any recommendations to patients or healthcare professionals on how to report immunogenicity-related adverse drug reactions. Furthermore, 80% of SmPCs do not–identify the assay used to assess the reported immunogenicity rates and 81% of SmPCs do not address the possible impact of immunogenicity on their drug's pharmacokinetics. It was also hypothesized based on these results that a group factor (i.e. SmPCs from older drugs) could be influencing how and which issues were being addressed by newer-drugs' SmPCs. To transform these documents into useful tools capable of providing answers when an immunogenic response occurs, a decision-tree addressing how to systematically report immunogenicity-related information in the SmPCs of biological products is proposed.

Conclusions: Based on these results, a case-by-case strategy does not yield sufficient reporting across SmPCs and thus reporting immunogenicity-related information should be reconsidered in order to report this information in a systematic way. Further guidance about reporting immunogenicity-related information is therefore required, otherwise SmPCs will not become the basis of information for healthcare professionals on how to use a biological product safely and effectively.

Keywords: Immunogenicity; Anti-Drug Antibodies; Summary of Product Characteristics; Biological Therapy; European Market

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Glossary

ADAs	Anti-Drug Antibodies
ADRs	Adverse Drug Reactions
ATC	Anatomical Therapeutic Chemical
BMWP	Biosimilar Medicinal Products Working Party
CTD	Common Technical Document
EEA	European Economic Area
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
HCPs	Healthcare Professionals
INN	International Nonproprietary Names
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
nAbs	Neutralizing Antibodies
PK	Pharmacokinetics
rDNA	Recombinant Deoxyribonucleic Acid
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

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Annex

1 Introduction

Unlike most small-molecules, biological drugs have the inherent possibility to trigger unwanted immunogenic responses against themselves, becoming an additional problem when analyzing their risk-benefit ratio. These unwanted reactions occur when foreignness or stress signals are perceived by the immune system [1], which responds by developing specific Anti-Drug Antibodies (ADAs). The clinical relevance of these ADAs is often unpredictable and historically it has ranged between no clinical relevance being detected up to life-threatening responses, with other consequences in-between these two extremes [2, 3]. To address this problem, European guidelines require the assessment of the immunogenic characteristics of new products for a successful Marketing Authorisation Application (MAA) [4].

Immunogenicity has been in the recent past one of the clinical issues that most frequently caused the rejection of MAAs because it was not sufficiently analysed [5], however the European Medicines Agency (EMA) has since published several guidelines about assessing and monitoring unwanted immunogenicity [4, 6, 7]. This guidance identifies the plethora of factors [4, 8] (disease-, patient- and product-related) that possibly promote unwanted immunogenicity, determines how to properly validate an assay to measure ADA development and establishes how to evaluate immunogenicity during clinical development. Furthermore, it also stipulates that the thoroughness of an analysis should be based on a risk-assessment strategy, which means that a deeper and detailed analysis is required for higher risk products [9]. These advancements support the notion that guidance on the data necessary to assess the immunogenicity of a new biological product is well-established [10]. Furthermore, a growing consensus between stakeholders has been achieved in recent years, benefitting the medical community by faster and methodical evaluations of MAAs [11].

Despite these advancements, it is still undefined which data should be included in the Summary of Product Characteristics (SmPC) and how should this information be reported. To solve this issue, a case-by-case analysis is currently performed but the quality of this approach is questionable [11]. This is problematic since SmPCs are one of the tools most commonly used by Healthcare Professionals [12] (HCPs) and since, according to European Guidelines, the SmPC should be “the basis of information for healthcare professionals on how to use the medicinal product safely and effectively” [13].

2 Objective

The objective of the current analysis is to scrutinize whether the current case-by-case practice leads to sufficient reporting of immunogenicity-related information in the SmPCs of biological products approved in the European market, thus raising a discussion on whether SmPCs are currently capable of guiding HCPs in the clinical practice and of promoting informed medical decisions [11, 14, 15].

3 Methods

3.1 Database of biological drugs

A list of all the biologic drugs approved by EMA until 2011 (inclusively) was compiled. Drugs approved after 2011 were excluded because newer drugs were expected to have less information about their immunogenicity reported in literature. Furthermore, this analysis investigates whether SmPCs had been updated after receiving a Marketing Authorisation (MA), which would not be a fair evaluation in drugs that have not been extensively used in real-world practice.

Published lists [16–19] were used to identify the biological drugs that were approved by either the Food and Drug Administration (FDA) and/or EMA. Concomitantly, an examination of all the titles obtained from searching recombinant DNA (rDNA) (701 results) and Biosimilar (filter:EPAR) (192 results) in EMA's search engine was performed. Each product identified through these sources was verified in EMA's website to confirm their current approval status.

3.2 Selection criteria

Selection criteria were defined to select the drugs that had a higher likelihood of including immunogenicity data in their SmPCs. The rationale for each criterion can be found in Annex Table A1. Briefly, the following criteria were used:

Exclusion criteria:

a. Exclusive indication(s) in Oncology, Rejection of transplants, Myocardial Infarction/Thromboembolism, Infertility;
b. Approval date later than 2011;

Inclusion criteria:

a. Biotechnological medicines;
b. Biosimilars of a.;
c. MA approved by EMA;

An article from GaBI Online[1] was also used to pinpoint any unidentified biosimilars.

A classification previously published by others [20] was used to categorize each drug in our list into different groups. This classification was proposed considering the categorizations given through the international nonproprietary names (INNs) and/or anatomical therapeutic chemical (ATC).

3.3 Identification & extraction of immunogenicity-related information from a SmPC

A collection of all the immunogenicity-related information detected inside the SmPCs was performed. To identify this data, a search inside each document for the keywords "antibodies/antibody", "neutralizing", "inhibitors", "immunogenicity", "batch" & "traceability" was performed. If this content had information relevant to the immunogenicity of the drug, it was extracted and compiled in an Excel sheet. The same keywords were used to identify the post-marketing alterations, accessible through the documents available in EMA's website as "Procedural steps taken and scientific information after the authorisation"

[1] *http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

3.4 Analysis of the immunogenicity-related information inside a SmPC

Based on the previously extracted information from SmPCs, dichotomous questions were devised to evaluate these documents on the most commonly reported and relevant issues related to immunogenicity. Table 1 contains these questions, their relevance and the elements that we were expecting to find in order to classify a SmPC as positively addressing each question. Idiosyncratic situations, that still raised doubts as to whether a SmPC positively addressed a specific question, were discussed with an independent researcher and a consensus was reached for each situation.

Table 1: Questions and rationale used to evaluate which issues are addressed in each SmPC

Questions	Objective	Rationale	Elements/Examples[a]
Q1	Does the SmPC report any data related to the immunogenicity of the drug?	Immunogenicity is a specific issue of biological drugs [1]. Thus, SmPCs of biological drugs should include product-specific information about this issue.	•Quantitative or qualitative information about the drug's immunogenicity
Q2	Does the SmPC report the immunogenicity rates for one or more clinical indications?	Immunogenicity rates give a sense to HCPs and patients about the frequency of ADAs development. While immunogenicity rates are not comparable between studies [10], they are still commonly reported and give a clearer sense about the immunogenicity of a drug [9] than a qualitative assessment.	•Incidence of ADA development •While prevalence rates could also be reported, we did not identify any situation where these results were included in the SmPCs
Q3	Does the SmPC mention the assay used to measure the development of ADAs on at least one of the reported immunogenicity rates?	The inclusion of immunogenicity rates has the possibility to influence the perception that HCPs have about the immunogenicity of a drug. This is a higher possibility in Europe, given that SmPCs are not required to state that immunogenicity rates between products are not comparable, unlike in the United States of America [11]. Despite this lack of comparability, immunogenicity rates are useful to easily convey how immunogenic a biological drug is. Given their utility, despite the variety of factors that can affect these results (which leads to the lack of comparison mentioned previously), we argue that they should always be contextualized by mentioning some of the relevant factors that can affect the immunogenicity rates being reported [9]. One of these factors is the assay used in the clinical trials [15]. The clear identification of the assay used to detect ADAs allows the HCPs to identify the advantages and disadvantages associated with said assay and determine how these might affect the results that are being reported. Thus, identifying the assay used to determine the immunogenicity rate of a product is relevant [11, 15] to diminish the likelihood of misconceptions from HCPs about the results being reported.	•Screening Assays such as: Direct ELISA; Indirect ELISA; Bridging ELISA; Electrochemiluminescence (with direct/indirect bridging format); Surface Plasmon Resonance; Radioimmunoprecipitation Assay; •Neutralizing Antibody (nAb) detecting assays such as: Cell-based bioassay; Competitive ligand binding assay

Q4	Does the SmPC mention the follow-up associated to at least one of the reported immunogenicity rates?	The sampling schedule is another particularly relevant issue when determining the immunogenicity of therapeutic proteins [4]. Thus, whenever reporting an immunogenicity rate, SmPCs should contextualize the results by concomitantly reporting the follow-up associated with it.	•Follow-up time
Q5	Does the SmPC identify any risk factor that may be associated with higher rates of immunogenicity/ higher rates of consequences associated with immunogenicity?	Depending on the effect that the immunogenicity might have on the risk-benefit ratio of a drug, the identification of risk factors in the SmPCs can be highly valuable for HCPs to be better informed when taking a medical decision. Since these factors are analysed in the pivotal trials for MA, the SmPCs should identify which factors were analyzed and which were identified as relevant factors to take into consideration during clinical practice.	•Quantitative or Qualitative information that identified risk factors such as Titer of ADAs; Disease; Genetic Factors; Dosage of the drug being administered; Concomitant Therapies; Drug Holidays; Isotypes of ADAs; Cross Reactivity with other drugs; Cross-Reactivity of ADAs with an endogenous peptide; Route of administration; •If a SmPC reported that a specific risk factor was tested but no significance was found, we still considered the SmPC as positively addressing Q5
Q6	Does the SmPC include any remark about characteristics of the ADA response?	Characteristics of the drug's immunogenicity are systematically evaluated during the centralized MAAs [4, 44] and are essential to contextualize the clinical relevance that the development of an immunogenic response might have	•Quantitative or qualitative information associated with characteristics of the immunogenic response. Examples include the Titer of ADAs; Affinity of ADAs against the drug; Transient/Persistent ADAs; Clearing/Sustaining ADAs; nAb status;
Q7	Does the SmPC mention the possible relationship (or lack thereof) between the development of ADAs and their impact on safety?	The impact that the development of an immunogenic response might have on the PK, efficacy or safety of a drug is highly idiosyncratic and unpredictable. This impact might range from no apparent clinical effect up to lack/loss of efficacy, increased/decreased effect due to the altered kinetics of the biologic drug or severe adverse ADRs [11]. Thus, whatever the relationship may be between immunogenicity and efficacy, safety or PK, it should be systematically addressed by all SmPCs where immunogenicity is of concern during the MAA [14]	•Quantitative or qualitative information about the clinical significance (efficacy, safety and PK) of the drug's immunogenicity
Q8	Does the SmPC mention the possible relationship (or lack thereof) between the development of ADAs and their impact on efficacy?	Same rationale behind Q7	•Quantitative or qualitative information about the clinical significance (efficacy, safety and PK) of the drug's immunogenicity
Q9	Does the SmPC mention the possible relationship (or lack thereof) between the development of ADAs and their impact on PK?	Same rationale behind Q7	•Quantitative or qualitative information about the clinical significance (efficacy, safety and PK) of the drug's immunogenicity

Q10	Does the SmPC have any recommendation on parameters to monitor because of immunogenicity?	The clear identification of parameters to monitor during clinical practice, that are associated with the development of a clinically relevant immunogenic response, is of major importance and utility to HCPs. Whenever applicable, a recommendation on the monitorization of specific parameters should be present in the SmPCs of biological drugs [4]. The inclusion of this type of recommendations is particularly relevant whenever a negative impact on the risk-benefit ratio of a drug is seen	•Recommendations on the monitorization of parameters related to the development of immunogenicity, such as: ADA status & Titer; nAb status & Titer; Drug Levels;
Q11	Does the SmPC include any recommendation on the clinical management of an immunogenic response?	The inclusion of clinical recommendations is especially relevant for drugs whose immunogenicity is associated with an impact on their risk-benefit ratio. Despite their usefulness, it can be hard to recommend specific strategies given that the consequences (and their intensity) of an immunogenic response can greatly vary between individuals and patient groups	•Clinical recommendations on appropriate decisions to take whenever the development of an immunogenic response impacts the risk-benefit ratio of a drug, such as: Stopping the administration of the drug; Increasing/Decreasing the administered dose; Administration of other support drugs;
Q12	Does the SmPC recommend the reporting of cases (by HCPs or patients) where immunogenicity is detected/ suspected?	The knowledge gathered during the pre-marketing phase about a drug's immunogenicity is limited [15], given the inherent limitations of these trials [4, 45] (Limited number of patients; Limited external validity) to detect long term and/or rare effects. Furthermore, the introduction of manufacturing changes can have an unforeseen impact on the immunogenicity of a drug. Thus, a solid pharmacovigilance system must be in place for HCPs and patients to keep trust in these products. This is reflected in the various guidelines related to pharmacovigilance or risk management plans. Given the relevance and utility of the pharmacovigilance system in keeping high standards of safety and efficacy, SmPCs should clarify when a report related to the development of immunogenicity is justified and what additional information is relevant to be included in this report.	•Identification of situations where a report by the HCPs or patients should be performed. These situations include: The confirmation of an ADA positive status; The development of clinical consequences (with an impact on safety or efficacy) previously associated with an immunogenic response;
Q13	Has the SmPC been updated with new information related to immunogenicity after the initial MA?	SmPCs are dynamic documents that must be updated throughout a products' market life. As previously mentioned, the knowledge about a drug's immunogenicity is limited before its use in the real world and further knowledge is gained and published as the experience with these drugs increases. SmPCs should be expected to reflect the knowledge that is obtained and accepted by the medical and academic communities, thus increasingly requiring updates as their real-world experience increases	•Identification of updates (reported in EMA's documents "Procedural steps taken and scientific information after the authorisation", specific for each drug) related to immunogenicity. Updates that were merely including immunogenicity data necessary for a new clinical indication were not considered as positive situations;

ADAs- Anti-Drug Antibodies; ADRs- Adverse Drug Reactions; ELISA- Enzyme Linked Immunosorbent Assay; EMA- European Medicines Agency; HCPs- Healthcare Professionals; MA- Marketing Authorisation;

MAA- Marketing Authorisation Application; nAb- Neutralizing Antibodies; PK- Pharmacokinetics; SMPC- Summary of Product Characteristics;

a- The examples are non-exclusive and represent the expected answers/information for each question. A case-by-case analysis was performed for each SmPC considering the context given in each document. Situations that did not fall under the scope of these examples were heavily discussed with an independent analyst until a conclusion was reached.

4 Results

A list of all the products that complied with our criteria had to be created. Afterwards, a classification proposed by other authors [20] was used to categorize these drugs into larger groups.

The motivation behind these exclusion and inclusion criteria was to select the drugs with the highest potential of developing unwanted immunogenicity since these drugs are expected to have a high degree of information in their SmPC regarding their immunogenicity and its relationship with the risk-benefit ratio. Annex Figure A1 shows that the majority (37/73) of the list is composed of Monoclonal Antibodies (mAbs), Insulins and Enzymes. Other groups that also consist of a considerable number of drugs are the Interferons, the Antihaemophilic Factors and the Epoetins. The full list of drugs can be accessed in Annex Table A2.

Despite having been identified and compiled into our list, Biosimilars are not included in further analyses due to the fact that a Biosimilar's SmPC in Europe should be identical (see Annex Table A2) to the SmPC of the reference product. If Biosimilars had been included in this evaluation, the results would therefore become invalid due to a bias caused by the duplicated analysis of some SmPCs. A dedicated section to the issue of Biosimilars and their SmPCs is presented in the discussion.

To analyze the immunogenicity data in the SmPC of each drug, a group of dichotomous questions was created. This 'questionnaire' can be seen in Table 1 and attempts to reflect the core immunogenicity-related topics that are addressed by these documents. These questions can be further divided into two groups: Group 1 consists of questions Q1-Q6 and its focus is on the degree of detail that is conveyed by the SmPCs about the risk of development of ADAs. The second group is composed of questions Q7-Q12 and its focus is on the information conveyed by the SmPCs regarding the clinical impact (and its management) of immunogenicity. Question Q13 does not fit any of these two groups

since it measures whether any new information about immunogenicity has been updated into the SmPCs.

4.1 Evaluation of SmPCs

Figure 1 shows the number of SmPCs that address each of the questions mentioned previously. To give a sense of proportion, the first column shows the total number of SmPCs that were analyzed. A clear distinction can be identified between the relevance across SmPCs that some topics have compared to others.

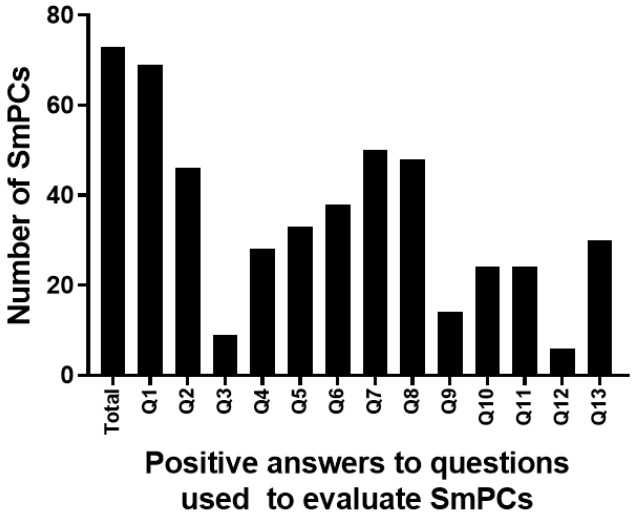

Figure 1 Number of SmPCs positively addressing each question raised in Table 1. SmPCs- Summary of Product Characteristics. Q1- Immunogenicity data; Q2- Immunogenicity rates; Q3- Assay; Q4- Follow-up; Q5- Risk factors; Q6- Characteristics of immunogenicity; Q7- Safety; Q8- Efficacy; Q9- Pharmacokinetics; Q10- Guidance on monitorization; Q11- Guidance on clinical management; Q12-Recommendations on reporting of cases; Q13- SmPCs updated

Looking at the first group of questions, Q1 demonstrates the importance of immunogenicity pertaining to biological drugs since 94% (68/72) of SmPCs include some degree of information about the drug's immunogenicity. Q2 shows that 37% (27/73) of SmPCs do not report any immunogenicity rates and thus this risk is not numerically quantified. Since Q3 and Q4 only make sense to be addressed when the immunogenicity rates are reported in the SmPCs, a drop (particularly intense for Q3) is seen. Q3 is related to the methodology that was used to detect the ADAs and only 20% (9/46), out of the

documents that report immunogenicity rates, concomitantly identify the assay used to measure the development of ADAs. A substantially higher proportion (61% [28/46]) of SmPCs concurrently report the follow-up associated with at least one immunogenicity rate. Looking at Q5 and Q6, we see that about half of SmPCs (45% [33/73] and 52% (38/73]) address these issues by respectively giving some complementary information related to risk factors and characteristics of the immunogenic responses that were identified or analyzed.

About the second group of questions (Q7-Q12), the majority of the SmPCs (70% [52/75) for Q7 & 67% [50/75] for Q8) contemplate the relationship (or lack thereof) that the development of immunogenicity may respectively have with the safety and efficacy of these drugs. On the other hand, sharply contrasting with the previous questions, 81% (59/73) of all SmPCs neglect to address Q9 by not mentioning the relationship (or lack thereof) between immunogenicity and the PK of these drugs.

Regarding the proportion of SmPCs issuing recommendations to address Q10, only 33% (24/73) of all SmPCs give any guidance to HCPs and patients, leaving the remaining SmPCs without any clarifications about the clinical circumstances that may justify monitoring the immunogenicity status of a patient or the drug's plasma levels. Q11 complements the previous question by analyzing if there are any recommendations to minimize the impact of immunogenicity on safety or efficacy. The same proportion of SmPCs as in Q10 was detected. As recognized in Table 1, Q10 and Q11 are questions that may not make sense to be addressed whenever a lack of relevance or knowledge about immunogenicity is detected. Since our analysis includes SmPCs in both situations, the proportion of SmPCs that are expected to address these issues is probably being underestimated.

A strong medical culture on reporting Adverse Drug Reactions (ADRs) whenever these occur is particularly important in biological drugs, given the impact that manufacturing changes might have on the risk-benefit ratio (through altered immunogenicity, for example) of a drug [21, 22]. Furthermore, given that uncertainty about the clinical relevance of immunogenicity of a biological product is a common problem after the MA [9, 15], it further increases the relevance of pharmacovigilance. Q12 evaluates the proportion of SmPCs that advise the HCPs or patients to report immunogenicity-positive cases (i.e. ADA positive patients) or cases where consequences related to

immunogenicity are suspected. Only 8% (6/73) of all SmPCs included recommendations of this kind, potentially hindering the perception of patients and of the medical community about the relevance of assessing and reporting these situations. To exemplify how SmPCs address Q10, Q11 and Q12, Annex Table A3 contains the statement from each SmPC that responds to these questions.

Finally, approximately 43% (30/70) of the SmPCs have had at least one post-marketing change to their SmPC that was associated with an update on immunogenicity data. Three drugs are excluded from this last analysis because they were approved nationally (Genotropin (somatropin), Eprex (epoetin alfa) and Neupogen (filgrastim)) and a justification for these exceptions be found in Annex Table A1.

Out of all the issues analysed, Q12 was the least addressed issue, followed by Q3 and Q9, respectively.

4.2 Detection of a group factor

Figure 2 further divides the positive answers according to the previously mentioned classification.

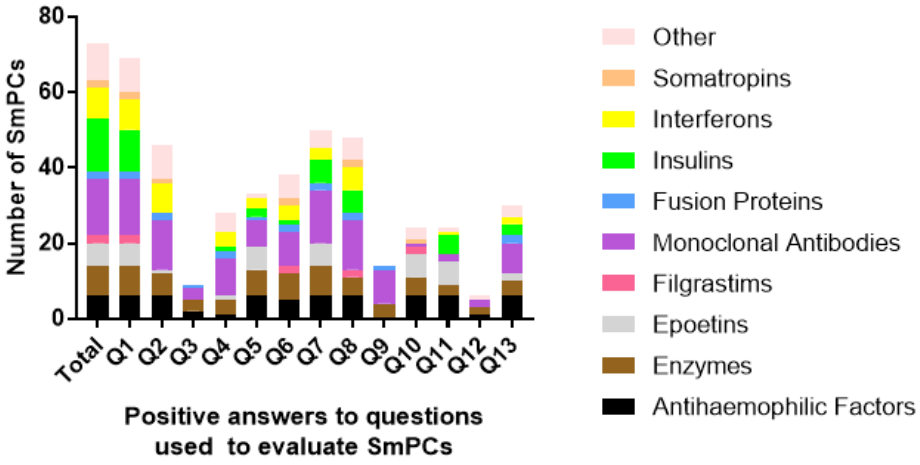

Figure 2 Number of SmPCs from each group positively addressing each question raised in Table 1. SmPCs- Summary of Product Characteristics. Q1- Immunogenicity data; Q2- Immunogenicity rates; Q3- Assay; Q4- Follow-up; Q5- Risk factors; Q6- Characteristics of immunogenicity; Q7- Safety; Q8- Efficacy; Q9- Pharmacokinetics; Q10- Guidance on monitorization; Q11- Guidance on clinical management; Q12-Recommendations on reporting of cases; Q13- SmPCs updated

This analysis shows a few trends that are possibly relevant to how immunogenicity results are being reported by the SmPCs: 1) In Q2, almost none of the SmPCs from Epoetins and Insulins reported any immunogenicity rates, which is peculiar given that the other groups address this issue in large proportions. Q4 and Q8 are other examples of similar situations. 2) The relationship between ADAs and the Pharmacokinetics (PK) (Q9) is only addressed by mAbs and Enzymes, which was not expected given the relevance that this relationship has for biotechnological drugs in general [11].

Overall, these trends lead us to suspect that previously published SmPCs could be influencing how the information is presented and which topics are addressed in the SmPCs of newer drugs from the same group, meaning that a group factor can be influencing how information about new drugs is being presented. While other factors (of which we are unaware) could explain these trends, further examples noticed during our analysis appear to support and validate this hypothesis:

1) A very small proportion of SmPCs include a statement to note that comparing the immunogenicity rates of different products is scientifically inappropriate. When these drugs were identified, it was noticed that they were abatacept, certolizumab pegol, golimumab, adalimumab and interferons beta-1a (Rebif and Avonex). These drugs are either mAbs (All of them are Anti TNF-α drugs except for abatacept, which has nonetheless the same indications) or Interferons-1b. The fact that this specific information is included in the SmPCs of drugs with the same indications appears to corroborate the hypothesis that a group factor is determining which information is presented by SmPCs.

2) Looking at the SmPCs of all human insulins, it becomes clear that the information about immunogenicity reported in all of them (excluding Insuman) is exactly the same across products. In all of these products, it is only mentioned that "No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed." [23–27]. This observation of equal information across SmPCs was also identified in Epoetins and Antihaemophilic Factors. A possible reason to explain this observation is that these drugs are commercially explored by the same MAH, however, this reason is not true for all of the products identified in these circumtances. Therefore, this observation also seems to be evidence that a group factor is influencing how immunogenicity data is reported by SmPCs.

5 Discussion

This analysis confirms the need to create a common framework for reporting immunogenicity-related issues that should be addressed by SmPCs. Several cases were identified where the data being reported was insufficient to inform the HCPs about the inherent immunogenicity of these biologicals. In other cases, data about immunogenicity was reported but not enough additional information of relevance was given to contextualize these results, creating the potential for misconceptions in the medical community about the immunogenicity of a specific product [11]. Furthermore, several signs suggest that a group-factor could be influencing how information is being reported in some SmPCs.

5.1 Least addressed issues by SmPCs

The first matter worth discussing arises from the least addressed questions that were identified through our analysis. As mentioned previously, Q12, Q3 and Q9 were unaddressed by 80% or more of the SmPCs that could have addressed these issues, which is from our point of view a lost opportunity to clarify HCPs and patients.

Regarding Q12, we were surprised to find that most SmPCs are not currently being used as a tool to promote the practice of reporting ADRs. The ADRs possibly related to the occurrence of an immunogenic response are especially relevant to be reported since this is one of the probable causes behind the occurrence of new ADRs after a manufacturing change occurs. Furthermore, if a causal link between an ADR and the occurrence of an immunogenic response is suspected/confirmed, other factors not usually asked to be reported could be relevant and the SmPC should clarify these aspects. We defend a pragmatic approach, where the reporter is expected to identify the ADA and the Neutralizing Antibodies (nAb) status of the patient (if determined), risk factors possibly associated with the occurrence of the immunogenic response and the cumulative exposure time. Other issues can possibly be relevant to report and should be considered in a case-by-case basis. While our analysis does not focus on other tools besides the SmPC, it's worth mentioning that current guidelines recommend including immunogenicity in the Risk Management Plan (RMP) (when identified as an important risk or as an area of missing information) of recently approved medicines and that other pharmacovigilance

tools can be further used as risk minimization strategies [15], overall contributing to the consolidation of a strong and reliable pharmacovigilance system for biological drugs.

Regarding Q3, immunogenicity rates are not comparable between studies. However, they provide useful estimates of how frequently immunogenicity occurs during real world usage, thus having the potential to influence HCPs on their perception of the immunogenic potential of a new biological medicine. One of the factors particularly relevant to consider when developing an immunogenicity assessment plan is the assay that will be used to measure the ADA status of the patients [9] and this factor alone can have a great impact on the immunogenicity rates of a product [29, 30]. We argue that not systematically including a recommendation about the inappropriateness of comparing immunogenicity rates from different studies in addition to not identifying the methodology used to measure the immunogenicity rates reported in the SmPCs has the potential to induce HCPs into relevant misunderstandings regarding the immunogenicity of biological products. The FDA acknowledges the relevance of this issue and currently recommends the inclusion of a statement about the inappropriateness of comparing cross-product immunogenicity rates in every product information [11]. Therefore, corrective measures in Europe are desirable in order to inform HCPs in a clear and transparent manner.

Another issue that our analysis detected is that the large majority of the SmPCs did not clarify whether the development of ADAs had an impact on the PK of these drugs. Non-neutralizing antibodies may affect the risk-benefit ratio of a drug by increasing (clearing ADAs) or decreasing (sustaining ADAs) a medicine's clearance rate [10, 31], possibly leading to a lack of efficacy or to an increase in frequency/severity of ADRs. In both cases, the impact surges because ADAs promote the drug's concentrations to be outside of the therapeutic window. Given this possibility, CTDs need to contain data about this relationship for a successful MAA [32] but the same standard in not applied in the SmPCs of biological drugs. Neglecting to report this information is, in our opinion, undermining the assessment of the HCPs regarding the impact of an immunogenic response.

5.2 Different regulatory regions, same problems?

Curiously, a previous study that analyzed the prescribing information of 121 biological drugs approved by FDA [33] reports equivalent proportions to our study regarding the drugs that address the clinical impact of immunogenicity on safety (60%), efficacy (49%)

and PK (26%). Despite not evaluating other issues, this comparability across studies raises the probability that the same or similar problems identified herein might also be applicable to other regulatory regions. Further analyses to the Product Information of biological drugs in these different regulatory regions is therefore appropriate to identify if the problems identified in this analysis are also common to other regulatory regions.

5.3 Proposal for reporting immunogenicity data systematically

Overall, we argue that the circumstances discussed above (i.e. important issues being left unaddressed and the possibility of a group factor) arise from a lack of guidance about reporting immunogenicity data. The current European guidelines clearly identify the requirements for immunogenicity assessment that must be fulfilled in the Common Technical Document (CTD) for a successful MAA [4, 14]. Furthermore, recently revised guidelines about Pharmacovigilance [7] issue more guidance about immunogenicity. On the other hand, sharply contrasting with these developments, very few clarifications have been published about the data that is expected to be reported in SmPCs. Therefore, while clear and specific guidance specifies the data that will be necessary for a successful MAA, the same cannot be said about which of this data should be transcribed into the SmPCs in order to inform HCPs and patients about the immunogenic potential of biological products. Considering that the immunogenicity of a drug has the potential to greatly affect the risk-benefit ratio of said medicine, not reporting or inconsistently reporting immunogenicity-related information hinders the capability of SmPCs to be "the basis of information for healthcare professionals on how to use the medicinal product safely and effectively" [13].

In order to transform SmPCs into useful tools when an unwanted immunogenic response occurs, we believe that the questions raised here should be addressed systematically. Our view, as schematized by Figure 3, is that each approved clinical indication should be associated with immunogenicity-related information from the pivotal clinical trials necessary to obtain the MA for said indication. This information should be sufficient to address Q2-Q9 if no clinically relevant impact has been verified in that clinical setting. However, if a relevant impact was detected, efforts should be pursued to also address Q10 and Q11. If Q2-Q9 have already been previously addressed and new data about immunogenicity is being added to update the SmPCs, we argue that at least Q2-Q4 should

be addressed in order to avoid the current practice of reporting immunogenicity rates without contextualizing these results in terms of the follow-up and assay used to determine these rates. When addressing these issues (especially those from the second groups of questions), the depth of analysis presented in the SmPCs should reflect the possible impact of the development of ADAs (*i.e.* with more information being expected when an impact is verified) thus mimicking the current risk-based analysis for drug development [14]. A recommendation on reporting ADRs related to immunogenicity should also be present once in every SmPC to promote a robust culture of pharmacovigilance. A parallel issue worth mentioning is the traceability of biological products. Current guidelines already recommend SmPCs to state that "(…)the name and batch number of the administered product should be clearly recorded" [7]. Our analysis only identified 20 out of 70 centrally approved products that included this statement in their SmPCs (data not shown) meaning that further efforts are necessary to systematically include this recommendation in all SmPCs of biological products.

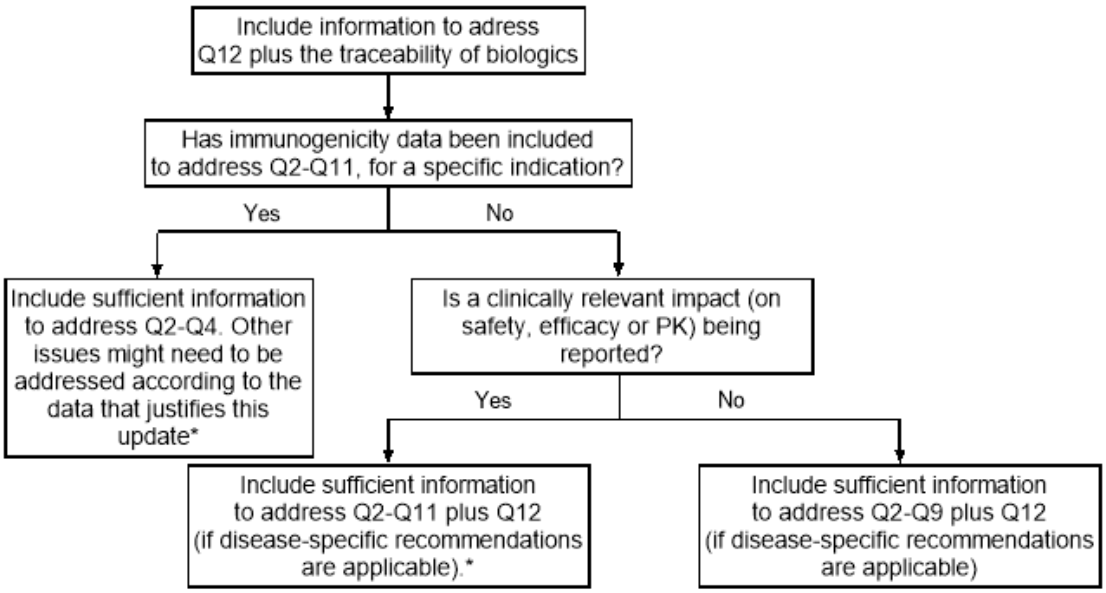

Figure 3 Decision tree of immunogenicity-related issues to address in a SmPC of a biological product whose immunogenicity is a potential issue. *The degree of information to address each question should be proportional to the impact of immunogenicity on the risk-benefit ratio of the drug. PK – Pharmacokinetics Q1- Immunogenicity data; Q2- Immunogenicity rates; Q3- Assay; Q4- Follow-up; Q5- Risk factors; Q6- Characteristics of immunogenicity; Q7- Safety; Q8- Efficacy; Q9- Pharmacokinetics; Q10- Guidance on monitorization; Q11- Guidance on clinical management; Q12-Recommendations on reporting of cases;

A potential problem with our proposal is that SmPCs should not address issues for which data is lacking [28]. However, several SmPCs were detected with a statement acknowledging the lack of data about immunogenicity for specific situations. Therefore, given the possible impact of immunogenicity on the risk-benefit ratio of biological drugs, we argue that a lack of knowledge for one (or more) of these issues is relevant information to be communicated and that these are the ideal situations to redirect HCPs and patients to the RMP and European Public Assessment Report (EPAR) of the product for more information.

5.4 Proportion of updated SmPCs

The third matter from our analysis worth considering is related to Q13. 43% of the SmPCs analyzed had at least one post-marketing change associated with immunogenicity. Therefore, this obviously implies that 57% of the biologic drugs that have been authorised prior to 2012 did not have their SmPC updated even once when it comes to data related to immunogenicity. Being a field in rapid development, especially regarding the methodologies used to detect ADAs [10], and considering that immunogenicity is appropriate to be included in the RMP of biological drugs when identified as an important risk or as an area of missing information, we were expecting that a much larger proportion of these older SmPCs (MA prior to 2012) had been updated. Therefore, one could ask whether new information about these drugs has been published and accepted by the scientific and medical communities which could have deserved an update of these SmPCs. While our analysis does not answer the previous question, it's undeniable that the immunogenicity rates of some SmPCs do not currently reflect the immunogenicity rates being published with newer and more sensitive assays. Given that these rates influence the perception of the medical community about how often the development of an immunogenic response against a biological drug occurs, we wonder if the SmPCs of older drugs should not be updated to also reflect the immunogenicity rates that are being detected with these newer assays instead of just reporting results based on assays developed 10-15 years ago. A perfect opportunity to update the information in some of these SmPCs arises from the approval of biosimilars.

5.5 Biosimilars' SmPCs and immunogenicity data

According to European guidelines, biosimilars are medical products comprised of a similar version to an active substance from an already established drug (reference product) in the European Economic Area (EEA). These biosimilar products must have proven a high degree of similarity (regarding their quality, biological and medical properties) between themselves and their reference products [7].

The Biosimilar Medicinal Products Working Party (BMWP) reported in 2012 three different possibilities regarding the inclusion of bioequivalence data into the SmPC of biosimilar drugs. These possibilities ranged from not including any information at all up to only reporting the bioequivalence data supporting EMA's assessment [34]. Current practice about a Biosimilar's SmPC in Europe is to develop a document identical (with the exception of using the INN of the active substance instead of the tradename of the reference product [35]) to the SmPC of the reference product, thus excluding any bioequivalence data.

Head to head studies comparing a biosimilar to its reference counterpart are a regulatory requirement. The low predictability that non-clinical models confer regarding the unwanted immunogenicity of biological drugs is one of the issues that contributes to the requirement of clinical studies for bioequivalence. Therefore, immunogenicity data is an important issue to analyze when determining the biosimilarity between two products. Furthermore, other issues possibly related to immunogenicity such as switching and extrapolation of indications are commonly raised by the scientific and medical communities regarding the use of biosimilars. While current practice is to include the details of the bioequivalence studies exclusively in the EPARs developed by EMA [35], we argue that this is an inadequate strategy given that low proportions of HCPs use EPARs as a source of information [12]. Furthermore, not including enough information about the bioequivalence studies in the SmPCs increases the likelihood of misunderstandings and unreasonable fears by some members of the medical community. On the other hand, the regulators' reasoning that different SmPCs between products with a similar active substance could lead to misunderstandings is also sensible [31]. Therefore, we propose a novel idea: The SmPCs of the reference product and of the biosimilar product should both be updated to include data from the bioequivalence studies, specifically the data related to the immunogenicity of both products.

From the reference products' perspective, we argue that this update is necessary given that most of these drugs have been on the market for over 10 years. During this period, an increasing number of improvements regarding the assessment of immunogenicity have occurred but the majority of SmPCs include data mostly obtained during the drug's pivotal clinical trials, as was shown in this analysis. Consequently, the immunogenicity rates reported by these documents are possibly underestimated in some drugs' SmPCs [1]. Our reasoning is that including the data from bioequivalence studies, assessed with new methodologies, could be an excellent opportunity to update these drugs' SmPCs thus providing a better sense of amplitude on the detected incidence of ADAs between studies. Moreover, including immunogenicity rates from the bioequivalence studies would almost surely require a concomitant statement about the incomparability between immunogenicity rates from different studies, which we also see as a positive outcome.

From the biosimilars' perspective, we argue that this update is necessary because several issues, including immunogenicity [36] but also switching/interchangeability [37, 38] and extrapolation of indications [31] have been raised throughout the years. Including immunogenicity data collected during the bioequivalence studies can help clarify some of these issues in a document that is regularly used by HCPs. Additionally, reporting data that supports the decision to approve a biosimilar into the European Market might help invalidate the perception that the evidence supporting this decision is insufficient [31], while excluding data from bioequivalence studies foments this perception.

Common updates to SmPCs of different biological products which contain the same or closely related active substance can be seen in several situations and examples of these include the updates A31/0134 and A31/0078 for moroctocog alfa (ReFacto AF) and octocog alfa (Advate and Helixate NexGen) respectively [39–41] or the update IB/0002/G for epoetin theta (Biopoin and Eporatio) [42, 43].

Applying the same principles, an update should also be required whenever a bioequivalence study between the pre and post-change versions of a product in humans is necessary. The arguments just mentioned for biosimilars are also applicable in these cases and we also think that including this data in the SmPCs of biological products raises awareness in the medical community about manufacturing changes that can have an impact on the risk-benefit ratio of the altered drug, further complementing the increased vigilance that is required after a change is proposed and approved [7].

5.6 Study Limitations

The focus of our analysis is not on the specific content presented in each SmPC, since such an analysis is out of the scope of this article. Instead, this evaluation is designed to identify which issues related to immunogenicity are not being addressed by the SmPCs, thus hindering the SmPCs of being the basis of information to HCPs. Given the inherent heterogeneity that exists across the SmPCs, the framing of each question was intended to be broad. Additionally, our decision-making process was based on a tolerant mindset, in which the bare minimum information about each question was enough to classify a SmPC as positively addressing the question. This permits the estimation of the maximum number of SmPCs that address these issues by excluding false negatives.

Two additional points of contention arise from this investigation. The first point is about the issues that were raised to evaluate the SmPCs. To reflect the "state of the art" on reporting immunogenicity data in SmPCs, all information about immunogenicity was collected before specifying any questions, thus allowing us to understand which issues were most commonly reported. This strategy explains why most questions are positively answered by 25% or more of the SmPCs analyzed. The second problem arises from evaluating whether a SmPC positively addresses each question, given its subjectivity. To mitigate this problem, several strategies were used. Firstly, the decision of whether a SmPC answered positively to each question was always performed by the same person. Secondly, expected elements for each question were identified *a priori*. Thirdly, discussions with an independent reviewer were performed for idiosyncratic situations.

Having made the case for the value of systematic reporting in order to inform prescribers, it is understandable that this may have relatively little influence on clinical management decisions, particularly with respect to use of biologicals that have been in clinical use for a long time. This is in large part because of the idiosyncratic nature of the clinical relevance of measurement of ADA. However, this information might become more relevant if data were made available regarding the proportion of ADA that are neutralizing versus the proportion of non-neutralizing antibodies. This would assume practical relevance in the context of clinical practice which includes measurement of trough levels of administered biologic and might have implications for dose optimization strategies.

6 Conclusions

This analysis focuses on the absence of a common set of problems related to immunogenicity that should be addressed by a drug's SmPC whenever said drug has the potential to develop clinically relevant ADAs. Currently, each SmPC reports the information that is considered as the most pertinent during the MAA, but this practice leads to a great degree of heterogeneity between SmPCs.

Given the clinical relevance that the development of ADAs might have, we argue that more guidance on how to report immunogenicity data is necessary. Until then, SmPCs of biological drugs will not be accomplishing their function as the basis of information for HCPs on how to use the medicinal product safely and effectively because a potentially impactful issue on the efficacy and safety of these products is not being adequately addressed by a large proportion of SmPCs. To contribute with solutions to this problem, a set of common issues necessary to be addressed is proposed. We hope that this tool can increase the quality and transparency of the information being reported in the SmPCs, thus promoting informed clinical decisions that increase the quality of care.

A specific analysis about biosimilars' SmPCs is also included, given their relevance in the current and future medical practice. Nowadays, SmPCs of biosimilar drugs are a complete reflection of the SmPCs of the reference product. We consider this practice to be unreliable given the relevance that some data from bioequivalence studies can have on clarifying some of the major issues that have been raised ever since biosimilars were introduced into the European market. We argue that reporting bioequivalence data into the SmPCs of the reference product and of the biosimilars that have been approved by EMA is a better alternative, with benefits to both products. The same strategy should also be applied to manufacturing changes that required bioequivalence studies in humans to be performed.

Despite this analysis and the several proposals recommended herein, the main purpose of this study was to diagnose a problem of communication caused by a lack of sufficient immunogenicity-related information in the SmPCs of biological drugs. We believe that addressing the issues raised in this analysis is responsibility of the regulatory agencies

and therefore urge regulatory clarification about these issues by including more guidance in future European guidelines or other appropriate sources. Guidance about reporting immunogenicity data on biological drugs' SmPCs will become ever more relevant given that increasingly greater numbers of biological products (including biosimilars) will be applying for MAs to the European Market.

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8 Annex

Table A1: Rationale for the eligibility criteria used to select the drugs with the highest potential of developing immunogenicity

TYPE OF CRITERIA	CRITERIA	RATIONALE
INCLUSION CRITERIA	a. Biotechnology-Derived medicines	Biological drugs consist of a wide variety of medicines, namely products derived from blood and plasma, drugs obtained from recombinant DNA technology, vaccines and advanced therapy medicinal products. Since most biologic medicines are developed using recombinant DNA (rDNA) technology, we were particularly interested in this group of drugs
	b. Marketing Authorization Application (MAA)	The MAA must have been evaluated by EMA and current status of the Marketing Authorization (MA) had to be classified as 'authorised' in EMA's website. We included in our analysis 3 exceptions to this rule, namely Genotropin, Eprex and Neupogen. In these cases, because a biosimilar has been approved by EMA, we compared the information in the SmPC of the reference drug (Available at Infarmed, Portugal's Regulatory Agency) with the info in the SmPC of the biosimilar, available at EMA's website. In all cases, we considered the information as comparable[a].
	c. Biosimilars	While Biosimilars were not included in our analysis since this would cause a bias in our results, we still collected and analysed their SmPCs to confirm that they had information aligned with the data in the SmPC of the reference drug. The analysis of the Biosimilars' SmPCs was independent of the Exclusion Criteria b, i.e, biosimilars approved after 2011 were still analyzed.
EXCLUSION CRITERIA	a. Authorization to use solely in: 1) Oncology 2) Rejection of Transplants 3)Myocardial Infarctions/ Thromboembolism 4) Infertility 5) Vaccines	The exclusion of these therapeutic areas was based on our assessment that immunogenicity would not be as relevant of an issue, either because a low degree of attention has been given by the medical/academic communities to the issue of immunogenicity (Oncology)[b] or because of the posology, i.e. usage in acute situations or highly immunosuppressed patients, therefore greatly limiting the possibility of immunogenicity development (Other areas). Vaccines were excluded because an immunogenic response was the intended effect.
	b. Concession of the MA after 2011	Right after obtaining a MA, there is a high degree of uncertainty regarding the immunogenicity potential (long-term effects, rare effects, sub-populations not

		evaluated in the pivotal trials) of a biological drug, which would increase the number of SmPCs not addressing the questions being evaluated if newer drugs would have been included in this analysis. Furthermore, the inclusion of Q13 implies that drugs with greater real-world experience were more likely to have needed an update. Thus, we limited our analysis to drugs that have been approved for a significant amount of time on the European market since we expect these to have consolidated information in their SmPCs.

MA = Marketing Authorization; MAA = Marketing Authorisation Application; rDNA technology = recombinant DNA technology; SmPCs= Summary of Product Characteristics

a- Since these drugs were not approved by EMA, they could not be found in EMA's search engine. Therefore, we did not find any documents reporting the "Procedural steps taken and scientific information after the authorization", meaning that we have no means of evaluating these SmPCs regarding Q13.

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Table A2: List of drugs divided by product class

Product class	INN	Brand name	Biosimilars
Antihaemophilic Factors	octocog alfa	Kogenate Bayer	Not Applicable
	octocog alfa	Helixate NexGen	Not Applicable
	octocog alfa	Advate	Not Applicable
	moroctocog alfa	ReFacto AF	Not Applicable
	eptacog alfa (activated)	NovoSeven	Not Applicable
	nonacog alfa	BeneFIX	Not Applicable
Enzymes	Imiglucerase	Cerezyme	Not Applicable
	Velaglucerase alfa	VPRIV	Not Applicable
	Alpha-Galactosidase A	Replagal	Not Applicable

	Alpha-Galactosidase B	Fabrazyme	Not Applicable
	alglucosidase alfa	Myozyme	Not Applicable
	α-L-Iduronidase	Aldurazyme	Not Applicable
	idursulfase	Elaprase	Not Applicable
	Galsulfase	Naglazyme	Not Applicable
Epoetins	Epoetin Alfa	Eprex/Erypo	-Epoetin Alfa Hexal -Binocrit -Abseamed -Retacrit -Silapo
	Epoetin Beta	NeoRecormon	Not Applicable
	epoetin theta	Eporatio	Not Applicable
	epoetin theta	Biopoin	Not Applicable
	darbepoetin alfa	Aranesp	Not Applicable
	methoxy polyethylene glycol-epoetin beta	Mircera	Not Applicable
Filgrastims	pegfilgrastim	Neulasta	-Ziextenzo -Pelmeg -Fulphila -Udenyca -Pelgraz
	Filgastrim	Neupogen	-Filgrastim Hexal -Nivestim -Accofil -Grastofil -Ratiograstim -Zarzio -Tevagrastim

Fusion Proteins	Etanercept	Enbrel	Not Applicable
	Abatacept	Orencia	Not Applicable
Insulins	Human Insulin	Actrapid	Not Applicable
	Human Insulin	Insulatard	Not Applicable
	Human Insulin	Insuman	Not Applicable
	Human Insulin	Protaphane	Not Applicable
	Human Insulin	Mixtard	Not Applicable
	Human Insulin	Actraphane	Not Applicable
	insulin lispro	Liprolog	Not Applicable
	insulin lispro	Humalog	Not Applicable
	insulin aspart	NovoRapid	Not Applicable
	insulin aspart	NovoMix	Not Applicable
	insulin glargine	Toujeo	Not Applicable
	Insulin Glargine	Lantus	-Semglee -Abasaglar
	Insulin Detemir	Levemir	Not Applicable
	Insulin Glulisine	Apidra	Not Applicable
Interferons	Interferon beta-1b	Betaferon	Not Applicable
	Interferon beta-1b	Extavia	Not Applicable
	Interferon beta-1a	Rebif	Not Applicable

	Interferon beta-1a	Avonex	Not Applicable
	Peginterferon alfa-2a	Pegasys	Not Applicable
	Peginterferon alfa-2a	ViraferonPeg	Not Applicable
	Peginterferon alfa-2b	PegIntron	Not Applicable
	interferon alfa-2b	IntronA	Not Applicable
Monoclonal Antibodies	Rituximab	Mabthera	-Rixathon -Rimixyo -Truxima -Blitzima -Rituzena -Ritemvia
	Pavilizumab	Synagis	Not Applicable
	Infliximab	Remicade	-Remsima -Inflectra -Flixabi -Zessly
	Adalimumab	Humira	-Hulio -Amgevita -Halimatoz -Imraldi -Hefyia -Hyrimoz -Idacio -Kromeya
	Omalizumab	Xolair	Not Applicable
	Natalizumab	Tysabri	Not Applicable
	Ranibizumab	Lucentis	Not Applicable

	Eculizumab	Soliris	Not Applicable
	Certolizumab Pegol	Cimzia	Not Applicable
	Ustekinumab	Stelara	Not Applicable
	Golimumab	Simponi	Not Applicable
	Canakinumab	Ilaris	Not Applicable
	Tocilizumab	RoActemra	Not Applicable
	Denosumab	Prolia	Not Applicable
	Belimumab	Benlysta	Not Applicable
Somatropins	somatropin	NutropinAq	Not Applicable
	somatropin	Genotropine	-Omnitrope
Others	anakinra	Kineret	Not Applicable
	Exenatide	Byetta	Not Applicable
	Exenatide	Bydureon	Not Applicable
	Liraglutide	Victoza	Not Applicable
	antithrombin alfa	ATryn	Not Applicable
	conestat alfa	Ruconest	Not Applicable
	teriparatide	Forsteo	-Movymia -Terrosa
	mecasermin	Increlex	Not Applicable
	pegvisomant	Somavert	Not Applicable
	Romiplostim	Nplate	Not Applicable

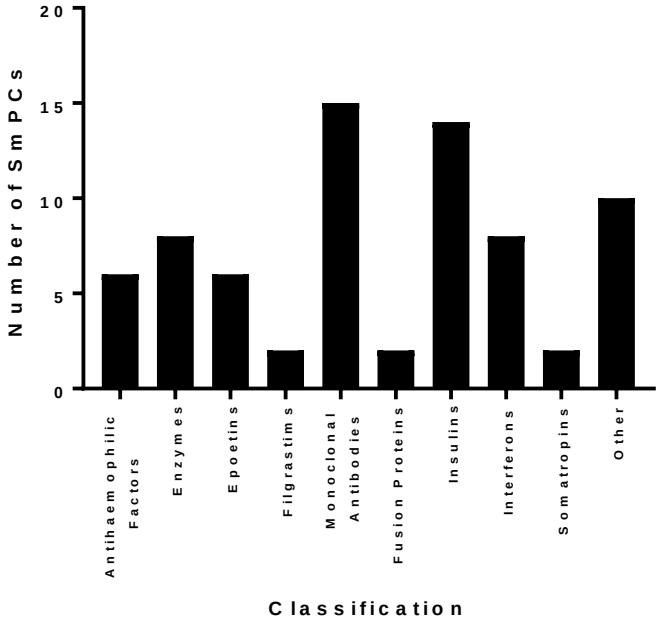

Figure A1: Number of SmPCs analyzed according to their classification. SmPCs- Summary of Product Characteristics

Table A3: Statements from each SmPC that respond to questions Q10, Q11 and Q12

Question	Drug	Example[a]
Q10- Does the SmPC have any recommendation on parameters to monitor because of immunogenicity?	Tysabri	Disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In these cases the presence of antibodies should be evaluated(…)
	Cerezyme	It is suggested that patients suspected of a decreased response to the treatment be monitored periodically for IgG antibody formation to imiglucerase.
	VPRIV	(...)in cases of severe infusion-related reactions and in cases of lack or loss of effect patients should be tested for the presence of antibodies(...)
	Fabrazyme	Antibody status should be regularly monitored
	Myozyme	IgG antibody titres should be regularly monitored
	Aldurazyme	Antibody status should be regularly monitored and reported
	Genotropine	Testing for antibodies to somatropin should be carried out in any patient with otherwise unexplained lack of response.
	Neulasta	If you experience a loss of response or failure to maintain a response with pegfilgrastim treatment, your doctor will investigate the reasons why including whether you have developed antibodies which neutralise pegfilgrastim's activity.
	Neupogen	If you experience a loss of response or failure to maintain a response with filgrastim treatment, your doctor will investigate

		the reasons why including whether you have developed antibodies which neutralise filgrastim's activity
	Kogenate Bayer	In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed.
	Helixate NexGen	In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed.
	Advate	In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed.
	ReFacto AF	In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed.
	NovoSeven	In case the factor VIIa activity fails to reach the expected level or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed.
	BeneFIX	(...)as with all factor IX products you should be carefully monitored for the development of factor IX inhibitors while being treated with BeneFIX.
	Eprex/Erypo	A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin alfa and perform antierythropoietin antibody testing.
	NeoRecormon	A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform antierythropoietin antibody testing.
	Eporatio	A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing.
	Biopoin	A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing.
	Aranesp	A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing.
	Mircera	A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing
	Increlex	Persons who have allergic reactions to injected IGF-1, who have unexpectedly high blood values of IGF-1 after injection, or who fail to show a growth response without any identified cause may be having an antibody response to injected IGF-1. This may be through the production of anti-IGF-1 IgEs, sustaining antibodies or neutralizing antibodies respectively. In such instances, instructions for antibody testing should be considered.
	Nplate	A loss of response or failure to maintain a platelet response with romiplostim treatment within the recommended dosing range

		should prompt a search for causative factors, including immunogenicity (…)
Q11- Does the SmPC include any recommendation on the clinical management of an immunogenic response?	Xolair	Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against omalizumab (…) Antihistamines and corticosteroids may be useful for preventing or treating this disorder(…)
	Tysabri	Given that efficacy may be reduced or the incidence of hypersensitivity or infusion-related reactions may be increased in a patient with persistent antibodies, treatment should be discontinued in patients who develop persistent antibodies.
	Cerezyme	Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions(...)If these reactions occur, immediate discontinuation of the Cerezyme infusion is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment are to be observed.
	Fabrazyme	Patients experiencing mild or moderate infusion-associated reactions when treated with agalsidase beta during clinical trials have continued therapy after a reduction in the infusion rate (~0.15 mg/min; 10 mg/hr) and/or pre-treatment with antihistamines, paracetamol, ibuprofen and/or corticosteroids.
	Aldurazyme	In clinical studies IARs were usually manageable by slowing the rate of infusion and by (pre-) treating the patient with antihistamines and/or antipyretics (paracetamol or ibuprofen), thus enabling the patient to continue treatment.
	Rebif	If a patient responds poorly to therapy with Rebif, and has neutralising antibodies, the treating physician should reassess the benefit/risk ratio of continued Rebif therapy.
	Insuman	Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.
	NovoRapid	Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.
	NovoMix	Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.
	Toujeo	Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper-or hypoglycaemia
	Lantus	Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia
	Kogenate Bayer	If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. & In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.
	Helixate NexGen	If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. &

		In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.
	Advate	In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors
	ReFacto AF	In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.
	NovoSeven	In case of severe bleeds the product should be administered in hospitals preferably specialised in treatment of haemophilia patients with coagulation factor VIII or IX inhibitors, or if not possible, in close collaboration with a physician specialised in haemophilia treatment
	BeneFIX	If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.
	Eprex/Erypo	A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin alfa and perform antierythropoietin antibody testing.
	NeoRecormon	In case anti-erythropoietin antibodymediated PRCA is diagnosed, therapy with NeoRecormon must be discontinued and patients should not be switched to another erythropoietic protein
	Eporatio	If typical causes of non-response are excluded, and the patient has a sudden drop in haemoglobin associated with reticulocytopenia, an examination of anti-erythropoietin antibodies and the bone marrow for diagnosis of pure red cell aplasia should be considered. Discontinuation of treatment with epoetin theta should be taken into account.
	Biopoin	If typical causes of non-response are excluded, and the patient has a sudden drop in haemoglobin associated with reticulocytopenia, an examination of anti-erythropoietin antibodies and the bone marrow for diagnosis of pure red cell aplasia should be considered. Discontinuation of treatment with epoetin theta should be taken into account.
	Aranesp	In case PRCA is diagnosed, therapy with Aranesp must be discontinued and patients should not be switched to another recombinant erythropoietic protein
	Mircera	In case PRCA is diagnosed, therapy with MIRCERA must be discontinued and patients should not be switched to another ESA
Q12- Does the SmPC recommend the reporting of cases (by HCPs or patients) where immunogenicity is detected/ suspected?	Xolair	(...) patients should be advised to report any suspected symptoms.
	Lucentis	Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation
	VPRIV	Antibodies may play a role in treatment-related reactions found with the use of velaglucerase alfa.To further evaluate the relationship, in cases of severe infusion-related reactions and in cases of lack or loss of effect patients should be tested for the presence of antibodies and the results reported to the company
	Aldurazyme	Antibody status should be regularly monitored and reported.
	Novo Seven	Development of inhibitory antibodies to NovoSeven has been reported in a post-marketing observational registry of patients with congenital FVII deficiency
	Nplate	If formation of neutralising antibodies is suspected, contact the local representative of the Marketing Authorisation Holder (…) for antibody testing

a- The examples given herein are non-exclusive and, in some SmPCs, other sections of these documents could possibly be given as examples that positively answer to Q10, Q11 or Q12.